REMARKS/ARGUMENTS

Claims 52, 54, 55 and 57-59 are pending in this application and stand rejected on various grounds. The title has been amended to more clearly reflect what is claimed in this application. The Examiner has additionally requested an update of the status of parent applications 09/953,499 and 09/254,465. Since the status update was already provided in the Amendment and Response dated July 11, 2005, no further amendment is deemed necessary. Claim 52 has been amended. Support for the amendment is, for example, at page 42, lines 17-20 of the specification. All amendments were made without disclaimer or prejudice, and are fully supported by the specification as originally filed, and do not add new matter. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications.

Claim Rejections – 35 U.S.C. §101

Claims 52, 54, 55, and 57-59 were rejected under 35 U.S.C. §101 because the claimed invention is allegedly "not supported by either a specific and/or substantial asserted utility of a well established utility for the reason of record."

In particular, the Examiner notes that the utilities, based on identifying PRO362 as a member of the immunoglobulin superfamily known as Junctional Adhesion Molecule (JAM) with homology to JAM, "are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for PRO362." In addition, the Examiner asserts that the ability of PRO362 to stimulate lymphocyte proliferation in the mixed lymphocyte reaction (MLR) assay of Example 5 does not support a specific and substantial utility for the claimed invention, essentially because the MLR assay "is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function" and thus "the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLR assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary." Finally, the Examiner asserts that one of ordinary skill in the art would conclude that a positive result in the inflammatory cell infiltrates into guinea pig skin assay described in Example 6 "indicates that the

polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic," and concludes that this Example "appears to be nothing more than a toxicity test and does not provide a real-world, readily available use."

Applicants respectfully disagree with the Examiner's lack of utility finding, and submit that the specification discloses at least one specific, substantial and credible asserted utility for the claimed PRO362 polypeptides.

First of all, Applicants note that the previous Office Action mailed on January 13, 2005 did not include a rejection for alleged lack of utility under 35 U.S.C. §101. Therefore, there are no "reasons of record" for the current claim rejections. Indeed, in the previous Office Action, Claims 55 and 57 were only objected to for being dependent on a rejected main claim, but were indicated as allowable if rewritten in independent form, including all limitations of the base claim and all intervening claims.

Turning to the current rejection, Applicants rely on the use of PRO362 and its claimed variants the treatment of inflammatory conditions and diseases to establish patentable utility. The anti-inflammatory activity of the claimed polypeptides is now recited in the claims. As the Examiner has acknowledged, this utility is disclosed at least at page 42, lines 17-20 of the specification. Since it is legally sufficient to provide one utility that meets the requirements of 35 U.S.C. §101, Applicants will not discuss the Examiner's comments on other asserted utilities, or the validity or significance of experimental data supporting such other utilities. However, this fact should in no way be construed as acquiescence to any part of the rejection, or to the Examiner's reasoning advanced in support of any part of the rejection. Nor should Applicants' focus on one specific utility in the present response be construed to mean that other utilities do not exist and/or are not sufficiently described in the specification.

Enclosed is a Declaration by Menno van Lookeren Campagne, Ph.D., a scientist at the Department of Immunology of Genentech, Inc., the assignee of the present application. Dr. van Lookeren Campagne is very familiar with PRO362, which has been extensively tested and studied in his laboratory, either personally by him or under his direct supervision. This work

included testing PRO362-Ig fusion proteins in two art recognized animal models of rheumatoid arthritis, namely the mouse model of collagen-induced arthritis (CIA) and the mouse model of antibody-mediated arthritis.

Paragraph 5 of the Declaration describes the preparation of a murine PRO362-Fc fusion protein generated by fusing the hinge, CH2 and H3 domains of murine IgG1 to the extracellular domain of murine PRO362. The amino acid sequence of murine PRO362 is shown in Exhibit B of the Declaration, while the nucleotide sequence of the murine PRO362-Fc fusion is shown in Exhibit C.

The protocol and results of the collagen-induced arthritis model experiments are described in paragraph 6 of the Declaration. The results show that treatment with the murine PRO362-Fc fusion protein: (1) resulted in significant reduction in joint swelling (Figure 1, Exhibit D); (2) inhibited joint inflammation (Figure 2, Exhibit E); (3) preserved cortical bone volume in the treated mice (Figure 3, Exhibit F); (4) did not alter the number nor the morphology of tissue resident macrophages (Figure 4, Exhibit G); (5) did not affect serum anti-collagen antibody titers (Figure 5, Exhibit H); and decreased the number of circulating inflammatory macrophages (Figure 6, Exhibit I).

The protocol and results of the antibody-mediated arthritis model experiments are described in paragraph 7 of the Declaration. The results show that treatment with the murine PRO362-Fc fusion protein: (1) prevented joint swelling following antibody-induced arthritis (Figure 8, Exhibit K); (2) reduced levels of inflammatory cytokines; and (3) inhibited joint inflammation (Figure 9, Exhibit L).

As Dr. van Lookeren Campagne summarizes in paragraph 9 of the Declaration, both the CIA and the antibody-mediated arthritis models have been used by many laboratories and are considered reliable animal models to test drug candidates for the treatment human rheumatoid arthritis. Based on the experimental findings detailed in the Declaration, Dr. van Lookeren Campagne states his considered scientific opinion that PRO362 is a "promising drug candidate for the treatment of rheumatoid arthritis." In addition, Dr. van Lookeren Campagne confirms

that the data, including the reduction of inflammatory cytokine levels, indicate that PRO362 is expected to be useful in the treatment of other inflammatory diseases and conditions as well.

It is well established that if the art is such that a particular model is recognized as correlating to a specific condition, then reasonable correlation will be accepted, unless the Examiner provides evidence that such correlation does not exist. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). A rigorous or an invariable exact correlation is not a requirement. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed Cir. 1985).

In particular, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. §2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that data generated in an established animal model, just as *in vitro* data, is acceptable to support utility as long as the data is "reasonably correlated" to the pharmacological utility described. Applicants submit that in the present case such reasonable correlation exists.

Since the data submitted with the attached Declaration of Menno van Lookeren Campagne directly support a specific and substantial asserted utility taught in the specification as filed, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 52, 54, 55, and 57-59 were rejected under 35 U.S.C. §112, first paragraph, on the ground that "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation."

In addition, the Examiner asserts that the specification "fails to provide any guidance as to how to make any isolated polypeptide having 95% amino acid sequence identity" to the amino acid sequences specifically disclosed, "where said polypeptide stimulates the proliferation of T lymphocytes" as recited in Claim 52. Thus, the Examiner finds that the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the inventive commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed January 13, 2005." In supporting this part of the rejection, the Examiner states that the disclosure of a single species and biological data obtained with that single species do not support an entire genus.

Applicants disagree and respectfully traverse the rejection.

As to the first part of the rejection, concerning the "how to use" prong of the enablement requirement, Applicants refer to the arguments and evidence submitted it addressing the previous "lack of utility" rejection. As the claimed invention complies with the utility requirement, one skilled in the art would know how to use the claimed invention so that it would operate as intended without undue experimentation. In view of this, since the scope rejection discussed below does not apply to Claims 55 and 57, at least those claims should be indicated as allowable, if rewritten as independent claims.

The Examiner's statement that the specification "fails to provide any guidance as to how to make any isolated polypeptide having 95% amino acid sequence identity" to the specific PRO362 sequence disclosed, is believed to be clearly in error. Methods for making polypeptide variants were well known in the art at the time the present invention was made. In addition, such methods are specifically described, for example, at page 20, lines 9-38 of the specification. Thus,

at the time the present invention was made, one of ordinary skill would clearly have known how to make PRO362 variants, based on general knowledge in the art and the teaching of the specification, without undue experimentation.

Positions for mutations without compromising biological activity could also have been identified, taking into account the structural information provided in the specification, *e.g.*, in Example 2, and further in view of the homology of the extracellular domain of PRO362 to that of JAM1 and the A33 antigen. Similarly to JAM family members, PRO362 is a type 1 transmembrane molecule and a member of the immunoglobulin superfamily. The extracellular domain of human PRO362 encodes both V and a C2 type terminal Ig domain. The C terminal cytoplasmic domains of human and murine PRO362 contain consensus AP-2 internalization motifs, and human and mouse PRO362 share 67% overall sequence homology with 83% homology residing in the IgV domain (see the mouse sequence attached to the van Lookeren Campagne Declaration). The presence of these motifs would have been readily recognized by those of ordinary skill in the art at the time the present invention was made.

One of ordinary skill would also have understood that sections of the PRO362 sequence, which show significant difference relative to other members of the family are more likely to contribute to unique biological properties of PRO362, not shared by other family members, while motifs shared or highly homologous to other members of the family are likely to participate in biological functions shared by the family members. In addition, sequences conserved between human and mouse PRO362 provide assistance in identifying sequences important for preserving biological activity.

One of ordinary skill would also have known how to test such variants to determine whether they exhibit anti-inflammatory activity, which is now recited in the genus claims. Animal models of inflammatory diseases, including arthritis, were well known and extensively used at the time the present invention was made, and are described at page 31, lines 11-29 of the specification. In addition, the data generated with murine PRO362 disclosed in the van Lookeren Campagne Declaration are evidence that extensive differences within the sequence are permissible without losing biological activity.

Accordingly, the reconsideration and withdrawal of the present rejection is respectfully requested.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1216 R1C1D1**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 14, 2006

By: _____
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